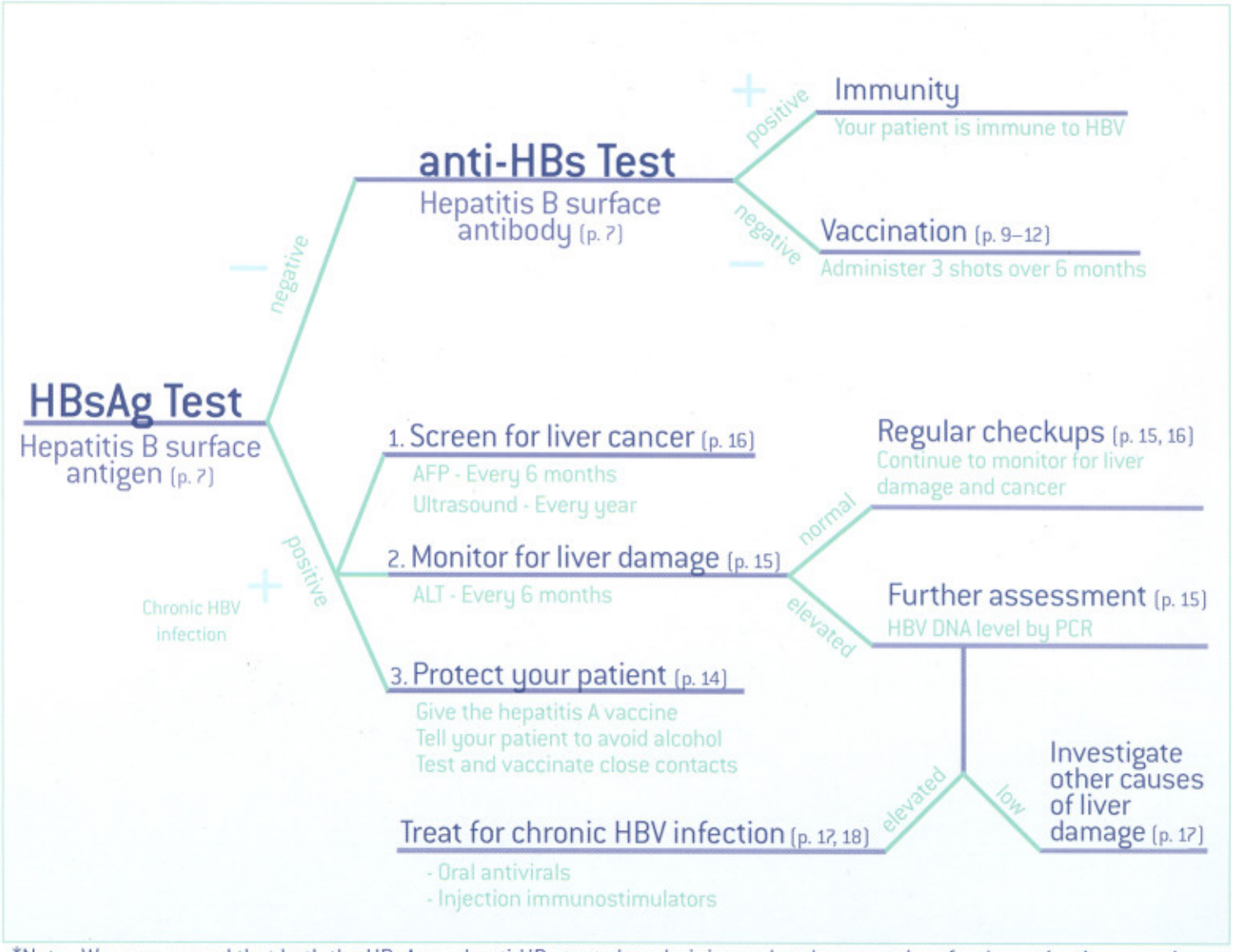
2007 Physician's Guide *to* Hepatitis B

a silent killer

Developed by the Asian Liver Center at Stanford University

Quick Summary: Chronic HBV Infection Diagnosis and Management



*Note: We recommend that both the HBsAg and anti-HBs tests be administered at the same time for the patient's convenience.

Unite against HBV.

The **Jade Ribbon** is folded like the Chinese character for people "人" symbolizing the united voices of those fighting hepatitis B and liver cancer worldwide.

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HBV and Liver Cancer Facts

As many as 1 in 10 Asians is chronically infected with HBV.

Without appropriate monitoring or treatment, 1 in 4 will die from liver cancer or liver failure.

HBV and liver cancer is the greatest health disparity between Asian and white Americans.

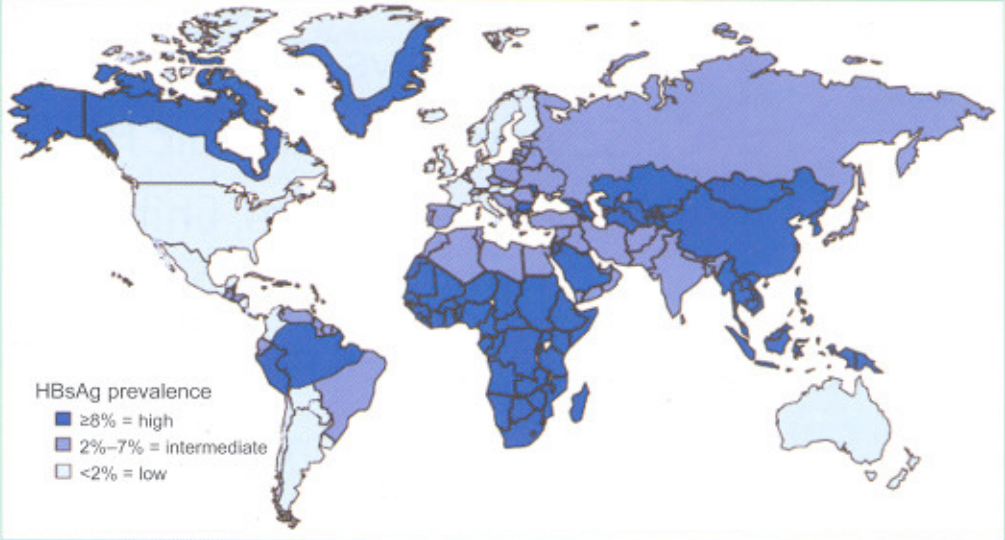
What is hepatitis B?

Hepatitis B is a serious infection of the liver caused by the hepatitis B virus (HBV), and can lead to premature death from cirrhosis (scarring of the liver), liver failure or liver cancer.

HBV is a global epidemic

- Although a safe and effective recombinant hepatitis B vaccine has been available since 1986, HBV still kills 700,000–1 million people every year worldwide.
- About 1 in 20 people in the world (370 million individuals) are living with chronic HBV infection.
- Without appropriate monitoring or treatment, 1 in 4 of those chronically infected will die from liver cancer or liver failure.
- Every 30–45 seconds, one person dies from this vaccine-preventable disease.

Geographic Distribution of Chronic Hepatitis B Virus Infection – Worldwide, 2005



Centers for Disease Control and Prevention. Available at http://www.cdc.gov/mmwr/PDF/rr/rr5416.pdf

HBV disproportionately affects Asian and Pacific Islanders (APIs)

- Of all the people with chronic HBV infection in the world, approximately two-thirds live in Asia, with 130 million in China alone.
- As many as 1 in 10 Asians and foreign-born Asian Americans is living with chronic HBV infection, compared to 1 in 1000 in the non-Asian U.S. population.
- Although Asian Americans make up only 4% of the U.S. population, they account for over half of the estimated 1.25 million individuals with chronic HBV infection.
- Liver cancer caused by chronic HBV infection is the second leading cause of cancer death for Asian men living in the United States.
- Liver cancer incidence is up to 9 times higher in Asian American men than in their white counterparts.
- Hepatitis B and liver cancer constitute the greatest health disparity between Asian and white Americans.

HBV is a silent killer

- Chronic HBV infection is dangerous because there are often no symptoms (even liver blood tests may be normal).
- As many as 2 out of 3 chronically infected persons are not aware they have been infected.
- By the time symptoms such as abdominal pain, abdominal distension or jaundice (dark urine and yellow discoloration of the skin or eyes) appear, it is often too late for treatment to be effective.
- The World Health Organization (WHO) estimates that about 90% of HBV-related deaths are associated with chronic HBV infection (70% from hepatocellular carcinoma with or without cirrhosis and 20% from cirrhosis), while less than 10% are associated with acute infection.

Regular screening for liver cancer in persons with chronic HBV infection can save lives.

HBV causes 60–80% of liver cancer cases worldwide

- HBV is a carcinogen that is second only to smoking tobacco in causing the most cancer deaths worldwide.
- Chronic hepatitis B infection is the leading cause of hepatocellular carcinoma (HCC), the most common type of primary liver cancer.
- People chronically infected with HBV have a 200-fold greater risk of developing liver cancer than those who are not infected.

Early detection of liver cancer is key

- Liver cancer is a silent killer because patients typically show no symptoms until the end stages of disease.
- Asians who are chronically infected by HBV at birth or during childhood may develop liver cancer as early as their teens.
- If diagnosed late, liver cancer is one of the most difficult cancers to treat. Even today, the 5-year survival rate remains <10%.
- Treatment options for liver cancer are limited. Currently, there is no effective systemic chemotherapy for liver cancer.
- However, early detection by regular screening can lead to successful surgical removal and long-term survival (p. 16).

Hepatitis B is preventable with a vaccine

The 3-shot hepatitis B vaccine can provide lifelong protection against HBV, thus eliminating the most common cause of liver cancer (p. 9–12).

- The hepatitis B vaccine is so effective at preventing HBV and liver cancer that the World Health Organization has declared it the world's **first "anti-cancer vaccine."**
- With awareness and proactive health practices, hepatitis B and liver cancer can be eliminated as a worldwide health problem.

How HBV is Transmitted

HBV is transmitted via infectious blood or semen. The modes of transmission can be easily remembered using the mneumonic "BBS": Birth, Blood, Sex.

Birth: Mother-to-child infection

HBV can be transmitted from a chronically infected mother to her child during the birthing process. This is one of the most common modes of transmission for Asians. Many pregnant mothers with chronic hepatitis B are unaware of their infection and end up silently passing the virus to the next generation.

Bloodborne infection

HBV can be transmitted through direct contact with infected blood. This includes:

- wound-to-wound contact
- reusing or sharing needles for tattoos, piercings, acupuncture or injection drugs
- reusing syringes or medical devices
- sharing razors or toothbrushes contaminated by blood
- blood transfusions

Sexually transmitted infection

HBV can be transmitted through unprotected sex with a person infected with HBV. The use of condoms can reduce, but not eliminate, the risk of infection. Vaccination remains the most effective way to protect against HBV (p. 9–12).

HBV vs. HIV/AIDS

In many Asian countries HBV is an even greater public health problem than HIV/AIDS.

There are 8–10 times more people in the world living with chronic HBV infection than with HIV/AIDS.

In the U.S., there are as many people living with chronic HBV infection as HIV/AIDS.

HBV can survive outside the body for 7 days, whereas HIV can survive for only a few hours outside the body.

HBV is 50–100 times more infectious than HIV.

HBV is NOT transmitted through food or water

There are many myths about how HBV is transmitted. A common misconception is that HBV can be spread through contaminated food or water, like the hepatitis A virus. This is not true.

HBV is NOT spread through:

- sharing food or water
- sharing eating utensils or drinking glasses
- tears, sweat, urine or stool
- coughing or sneezing
- hugging or kissing
- breastfeeding
- mosquitoes

Do not discriminate against people with HBV

There is no reason to distance yourself from people infected with HBV. People with chronic HBV infection should not be excluded from work, school or other daily activities.

Acute vs. Chronic HBV Infection

3 possible outcomes after initial HBV infection

1. Acute hepatitis B resulting in fulminant liver failure

Infection with HBV causes extensive liver cell death resulting in liver failure and sometimes death. Fortunately, this most severe form of acute hepatitis is uncommon, occurring in only 0.5–1% of hepatitis B cases.

2. Acute hepatitis B with full recovery and development of immunity

HBV is spontaneously cleared from the body within a few months and immunity against future infection develops. There is currently no FDA-approved drug treatment for acute infection and the main form of therapy is supportive care.

3. Chronic hepatitis B

Failure to clear the initial HBV infection will result in a chronic (lifelong) infection. There are six FDA-approved drugs to treat chronic HBV infection, but regular screening for liver damage and cancer is needed to determine if drug therapy is necessary. Without appropriate monitoring or treatment, 1 in 4 chronically infected persons will die from cirrhosis, liver failure or liver cancer.

Symptoms of acute HBV infection include:

- jaundice
- fatigue
- nausea
- abdominal pain
- loss of appetite

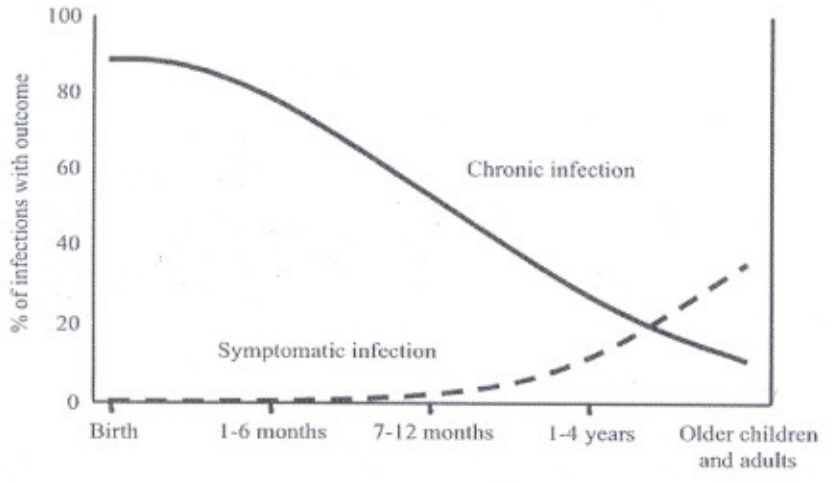
People with chronic HBV infection usually exhibit NO SYMPTOMS until they have developed cirrhosis or advanced liver cancer.

Children are more likely than adults to develop chronic HBV infection, while newly infected adults are more likely to have symptomatic infections.

Newborns are most vulnerable to chronic infection

Anyone who is not protected against HBV can become infected. However, newborns and young children who become infected with HBV have the greatest risk of developing a lifelong infection. As many as 90% of infected newborns develop chronic hepatitis B. This is why it is important for all newborns to be vaccinated against HBV at birth (p. 13). When infants and children are infected, they usually exhibit no or few symptoms. When *adults* are infected, 30–50% are likely to become ill with symptoms of acute infection (e.g. fatigue, loss of appetite or jaundice), but the risk of developing lifelong infection is less than 10%.

Outcome of hepatitis B virus infection by age at infection



World Health Organization. http://www.wpro.who.int/health_topics/hepatitis_b/publications.htm

Screening for Chronic HBV Infection

Since up to 10% of foreign-born APIs unknowingly have chronic HBV infection acquired since early childhood, it is prudent and important to check for HBsAg and anti-HBs before vaccination.

HBV screening is important!

Many chronically infected persons show no outward signs of HBV infection, therefore screening for hepatitis B is necessary to:

- Identify individuals who have chronic HBV infection so they can receive appropriate medical management;
- Identify those who are unprotected so they can be vaccinated; and
- Avoid unnecessary vaccination (and help reduce costs). Vaccination is *not* beneficial for patients already chronically infected with HBV, or already immune (either through prior vaccination or a previous resolved acute infection).

HBV screening is a simple blood test for the following markers:

1. Hepatitis B surface antigen (HBsAg)

The HBsAg test is the ONLY way to definitively diagnose chronic HBV infection. By definition, if your patient remains HBsAg-positive for more than 6 months, then he/she has developed chronic (lifelong) infection. Since most Asians became infected at birth or during early childhood, most of your Asian patients who test positive for HBsAg will have chronic HBV infection. HBsAg-positive patients require counseling and medical management for chronic HBV infection to reduce their risk for chronic liver disease (p. 14–18).

2. Hepatitis B surface antibody (anti-HBs)

The anti-HBs test will tell if your patient is protected against HBV. Anti-HBs can be produced in response to vaccination or recovery from an acute hepatitis B infection.

Quick Test Results

Result	Interpretation
HBsAg (+) anti-HBs (-)	Chronic HBV infection*
HBsAg (-) anti-HBs (+)	Immune to HBV
HBsAg (-) anti-HBs (-)	Unprotected; Need vaccination
HBsAg (+) anti-HBs (+) (rare)	Chronic HBV infection*

*If HBsAg remains positive for 6 months

Who should get screened for HBV?

2006 guidelines from the Centers for Disease Control and Prevention (CDC) call for routine HBV screening of all foreign-born persons from high endemic areas (see box on right) *regardless of their immunization history*. This includes immigrants, refugees, asylum seekers, and internationally adopted children.

Other groups recommended for HBV screening include:

- Household, sex, and needle-sharing contacts of HBsAg-positive persons;
- Pregnant women;
- HIV-infected persons; and
- Hemodialysis patients.

The CDC recommends routine HBV screening for all persons born in high* endemic regions:

Africa
Asia and Pacific Islands
Caribbean (Turks and Caicos)
Eastern Europe
Middle East (Saudi Arabia and Jordan)
South America (Amazon Basin)
Alaska, Northern Canada, and Greenland (indigenous populations)

*HBsAg prevalence of ≥ 8%

For a complete list refer to the CDC. *http://www.cdc.gov/mmwr/PDF/rr/rr5516.pdf*

What can physicians do to increase screening?

If you are seeing the patient for the first time, ask whether they are foreign-born or have a foreign-born parent. If so, screen for HBsAg and anti-HBs. If they are not infected and not protected, start the hepatitis B vaccination series (p. 9). In addition, you can help raise awareness about hepatitis B by having educational brochures in the waiting area and around the office for people to pick up (p. 22).

What about hepatitis B core antibody (anti-HBc) blood tests?

Some HBV blood panels may include two additional tests:

- The **total hepatitis B core antibody (total anti-HBc) test** tells if your patient has been previously infected with HBV, which is useful for screening potential blood donors (the U.S. does not allow people with past HBV infections to donate blood – even if they have recovered). The test by itself does not tell if your patient is protected against HBV infection.
- The **hepatitis B core IgM antibody (IgM anti-HBc) test** tells if an unprotected patient has recently been infected with HBV.

Anti-HBc tests indicate current or past HBV infection, but only the HBsAg test can identify chronic HBV infection.

Only order the IgM anti-HBc test if you suspect your patient recently became infected with HBV (e.g. through a needlestick injury or sexual contact with an HBV-infected person).

Blood Test	Result	Interpretation
Total anti-HBc	Positive (+)	Was infected with HBV (the test alone does not tell if immunity or chronic infection has developed)
	Negative (-)	Never been infected with HBV; Candidate for donating blood
IgM anti-HBc	Positive (+)	Recently acquired acute HBV infection

A positive total anti-HBc test or IgM anti-HBc test does *not* tell if your patient has chronic HBV infection – only an HBsAg test that remains positive for over six months can do this. If your patient has acute HBV infection, his/her infection may or may not become lifelong.

Vaccinating Infants, Children & Adults

Anyone who has not already been vaccinated or infected should be offered hepatitis B vaccination.

Travelers to high[1] and intermediate[2] endemic regions should be vaccinated:

Africa
Asia & Pacific Islands
Caribbean
Central America
Eastern Europe
Middle East
South America
Western Europe (Greece, Malta, Portugal, Spain)
Alaska, Northern Canada, & Greenland (indigenous populations)

[1] HBsAg prevalence of ≥8%.
[2] HBsAg prevalence of 2–7%.

For a complete list refer to the CDC. *http://www.cdc.gov/mmwr/PDF/rr/rr5516.pdf*

3-for-Life

The hepatitis B vaccine is safe and >95% effective at preventing HBV infection. Vaccination involves a series of 3 shots given over 6 months, and can provide lifelong immunity against HBV. The hepatitis B vaccine is so effective at preventing HBV infection and liver cancer that it is known as the world's **first "anti-cancer vaccine."** No booster shots are recommended by the CDC. The vaccination series can be started at any age. For people who have fallen behind schedule, the series may be continued without starting over. The usual schedule is as follows:

1st shot —1 month→ **2nd shot** —5 months→ **3rd shot**

Who should get vaccinated against HBV?

The CDC recommends universal vaccination of all newborns and previously un-vaccinated children and adolescents. Adult immunization is recommended for:

- **Anyone seeking protection from HBV infection**;
- Household, sex, and needle-sharing contacts of HBsAg-positive persons;
- Healthcare and public safety workers;
- Injection drug users;
- Those with more than one sex partner;
- Men who have sex with men;
- Those infected with HIV and/or other sexually transmitted diseases;
- Those with end-stage renal disease or chronic liver disease; and
- Travelers to regions with high or intermediate HBsAg prevalence (see box on left).

Who should get tested after vaccination?

After completing the vaccination series, most people do not need to be tested for anti-HBs to confirm protection against HBV. However, the following high-risk groups should receive post-vaccination testing:

- **Infants born to HBsAg-positive mothers**
  Test for both HBsAg and anti-HBs at age 9–18 months of age.

- **Healthcare and public safety workers; immunocompromised persons (e.g. HIV/AIDS, hemodialysis patients); sexual partners of HBsAg-positive people**
  Test for anti-HBs 1–2 months after completion of the vaccination series.

If your patient is NOT immune after vaccination

Although uncommon, about 5% of people who complete the hepatitis B vaccination series may not acquire immunity (anti-HBs levels are <10 mIU/mL). In these cases, take the following steps:

1. Administer another 3-shot series at the normal schedule using a different hepatitis B vaccine (p. 10).
2. Test again for anti-HBs 1–2 months after completion of the series to confirm protection. 44–100% of these patients will successfully develop immunity.

The rare group of people not protected after six doses should take care to avoid HBV transmission (e.g. cover wounds, use condoms). Nonresponders exposed to HBV-infected bodily fluids should get the hepatitis B immune globulin (HBIG) shot to prevent infection (p. 10).

Hepatitis B Vaccines

Engerix-B and Recombivax HB: HBV only

For any age: These single-antigen hepatitis B vaccines are typically given as a 3-shot series. For adolescents 11–15 years old, an alternative 2-dose Recombivax HB regimen may be used. Engerix-B and Recombivax HB can be used interchangeably and administered concurrently with hepatitis B immune globulin (HBIG) or other vaccines.

Free vaccines for children

Hepatitis B vaccine is free for children 0–18 years of age who are on Medicaid or whose vaccinations are not covered by insurance. These vaccines can be obtained through the federal Vaccines for Children program. For more information, visit http://www.cdc.gov/nip/vfc.

Combination Vaccines

Pediarix: HBV + diphtheria + tetanus + pertussis + polio

For children (6 weeks–7 years of age): All newborns, regardless of their mother's HBsAg status, should receive a birth dose of the hepatitis B vaccine with either Engerix-B or Recombivax HB. After the initial birth dose, a 3-dose Pediarix regimen can be used to complete the series.

Comvax: HBV + Haemophilus influenza type B

For children (6 weeks–6 years of age): All newborns, regardless of their mother's HBsAg status, should receive a birth dose of the hepatitis B vaccine with either Engerix-B or Recombivax HB. After the initial birth dose, a 3-dose Comvax regimen can be used to complete the series.

Twinrix: HBV + hepatitis A

For adults (18 years of age and older): Suitable for anyone seeking protection from HBV and/or hepatitis A virus (HAV), and high risk groups such as travelers to countries of high endemicity, men who have sex with men, injection drug users, medical or laboratory workers handling HBV or HAV, and patients with chronic liver disease. Whereas hepatitis B vaccine is usually given in three shots and hepatitis A vaccine is given in two shots, Twinrix is given as a 3-shot series.

Postexposure prophylaxis

HBIG (Hepatitis B Immune Globulin)

For any age: Provides passively acquired anti-HBs and temporary protection against HBV infection (i.e. 3–6 months). HBIG is typically administered along with hepatitis B vaccine *after* unvaccinated persons are exposed to blood or bodily fluids infected with HBV (e.g. when infants are born to HBsAg-positive women, after needlestick injuries, and after sexual contact with an infected person). HBIG alone is the primary means of protection for nonresponders to hepatitis B vaccine.

Adult Vaccine Schedules			
	Hepatitis B Vaccines		HBV + HAV vaccine
	Engerix-B	**Recombivax HB**	**Twinrix**[1]
Adults (≥20 yrs)	0 mo: 1st dose 1 mo: 2nd dose 6 mo: 3rd dose	0 mo: 1st dose 1 mo: 2nd dose 6 mo: 3rd dose	0 mo: 1st dose 1 mo: 2nd dose 6 mo: 3rd dose
Immunocompromised[2] **Adults (≥20 yrs)**	0 mo: 1st dose 1 mo: 2nd dose 2 mo: 3rd dose 6 mo: 4th dose 7-8 mo: Test for anti-HBs	0 mo: 1st dose 1 mo: 2nd dose 6 mo: 3rd dose 7-8 mo: Test for anti-HBs	0 mo: 1st dose 1 mo: 2nd dose 6 mo: 3rd dose 7-8 mo: Test for anti-HBs

[1] Twinrix may be given to adults ≥18 years old.
[2] E.g. Patients undergoing hemodialysis or chemotherapy, or HIV-infected persons. Higher doses are recommended (Engerix-B: 40µg/2.0mL, Recombivax HB: 40µg/1.0mL).

Pediatric Vaccine Schedules			
	Hepatitis B Vaccines	Combination Vaccines	
	Engerix-B or Recombivax HB	**Pediarix**	**Comvax**
Infants (0-1yr) with HBsAg(–) mother	Birth[3]: 1st dose 1-2 mo: 2nd dose 6 mo: 3rd dose	Birth[3]: Eng/Rec[4] 2 mo: 2nd dose 4 mo: 3rd dose 6 mo: 4th dose	Birth[3]: Eng/Rec[4] 2 mo: 2nd dose 4 mo: 3rd dose 12-15 mo: 4th dose
Infants (0-1yr) with HBsAg(+) mother	Birth[3]: 1st dose + HBIG[5] 1-2 mo: 2nd dose 6 mo: 3rd dose 9-18 mo: Test for HBsAg, antiHBs	Birth[3]: Eng/Rec[4] + HBIG 2 mo: 2nd dose 4 mo: 3rd dose 6 mo: 4th dose 9-18 mo: Test for HBsAg, anti-HBs	Birth[3]: Eng/Rec[4] + HBIG 2 mo: 2nd dose 4 mo: 3rd dose 12-15 mo: 4th dose 18 mo: Test for HBsAg, anti-HBs
Children and Adolescents[6] **(1-19 yrs)**	0 mo: 1st dose 1 mo: 2nd dose 6 mo: 3rd dose	--	--

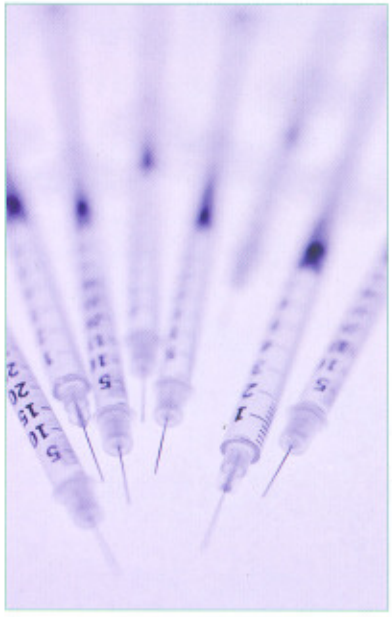
[3] Within 12 hours of birth.
[4] Either Engerix-B or Recombivax HB should be used for the birth dose.
[5] Hepatitis B immune globulin (0.5mL) administered intramuscularly in a separate site from vaccine.
[6] For adolescents (11–15 years), an alternative 2-dose Recombivax HB regimen may be given at 0 and 4–6 months.

Notes regarding preterm infants weighing less than 2000 grams:

- For premature infants born to HBsAg-negative mothers: Delay administration of the vaccine series until age 1 month or hospital discharge, then resume the series according to the schedule.
- For premature infants born to HBsAg-positive mothers: Give the HBIG shot and HBV vaccine within 12 hours of birth, then start the vaccine series beginning at age 1–2 months (do not count birth dose as part of the vaccine series).

Modified from Centers for Disease Control and Prevention. A Comprehensive Immunization Strategy to Eliminate Transmission of Hepatitis B Virus Infection in the United States.

Vaccine Administration and Storage



Follow these simple precautions to protect your patients:

- **Shake the vaccine before use.** Hepatitis B vaccine normally looks cloudy, but if the vaccine stands for a long time, it may separate from the liquid and look like fine sand at the bottom of the vial.

- **Do NOT freeze or expose to freezing temperatures.** Store hepatitis B vaccine at 2–8°C (36–46°F). The "shake test" will determine if the vaccine has been damaged by freezing. If the vaccine fails the shake test (the vaccine and liquid do not mix) you must discard it.

- **Administer the hepatitis B vaccine intramuscularly** (i.e. in the arm for children and adults, and in the thigh for infants). It is ineffective if given subcutaneously in fatty tissue (i.e. in the buttocks).

- **Do NOT reuse needles.** Always use sterile syringes, preferably with auto-disable features to prevent reuse.

- Immediately dispose of used needles into puncture-resistant safety containers.

Avoiding Needlestick Injuries

How to protect yourself:

- Practice universal precautions to prevent transmission of HBV and other bloodborne pathogens, including safe needle handling and the use of gloves.
- Vaccinate all health care workers against HBV, then test for anti-HBs 1–2 months after completion of the vaccination series to confirm protection (anti-HBs level ≥ 10mIU/mL).

What to do if you are exposed to HBV-infected blood through a needlestick or other sharps injury:

- **If you have already developed immunity from prior vaccination or resolved infection** (anti-HBs level ≥ 10mIU/mL):
  No treatment is necessary.
- **If you are unvaccinated, have not completed the 3-shot series, or are unsure of your vaccination status:**
  1. Get the HBIG shot (0.06mL/kg) within 24 hours of exposure;
  2. Complete the hepatitis B vaccination series on schedule; and
  3. Test for HBsAg and anti-HBs 1–2 months after the last dose of hepatitis B vaccine.

HBV Testing in Pregnant Women

FAQs for Moms-to-Be

Is breastfeeding safe?
HBV is not transmitted through breast milk. Breastfeeding is safe for all newborns, regardless of the mother's HBV status.

Can C-sections prevent HBV?
Cesarean sections cannot prevent HBV transmission from mother to child. Hepatitis B vaccination plus the HBIG shot is the best way to protect newborns against HBV.

Can women with chronic HBV infection be treated during pregnancy?
HBV treatment is currently not recommended during pregnancy.

All pregnant women should be tested for HBsAg

Federal guidelines recommend that all pregnant women be tested for HBsAg at an early prenatal visit (i.e. in the first trimester) during each pregnancy, even if they have been previously tested or vaccinated. The CDC Advisory Committee on Immunization Practices also recommends the following:

If your pregnant patient is HBsAg-negative and anti-HBs-negative:

- Send a copy of the lab report documenting the woman's HBsAg status to the birth hospital.
- Provide the hepatitis B vaccine. The vaccine is safe even when given during pregnancy.

If your pregnant patient is HBsAg-positive:

- Send a copy of the lab report documenting the woman's positive HBsAg status to the birth hospital.
- Send another copy of the lab report to the local health department for case management (reporting all HBsAg-positive cases is required by law in most states).
- Emphasize to the expecting mother the importance of having her newborn receive HBIG and the birth dose of hepatitis B vaccine to prevent perinatal hepatitis B transmission.

All newborns should be vaccinated at birth

Federal guidelines recommend that all newborns be vaccinated against HBV at birth, regardless of the mother's HBV status. It is important for all newborns to complete the hepatitis B vaccination series to receive lifelong protection against HBV. See page 11 for the vaccine schedule.

Infants born to women with chronic HBV must also receive the HBIG shot at birth

Without immunoprophylaxis, infants born to HBsAg-positive mothers are at the highest risk of developing chronic HBV infection. Therefore they must:

- Receive the first dose of hepatitis B vaccine ***and*** the HBIG shot within 12 hours of birth.
- Complete the vaccine series.
- Be tested at 9–18 months of age for HBsAg and anti-HBs to confirm protection against HBV.

Timely vaccination will be more than 95% effective in protecting the newborn against HBV infection. See page 11 for the vaccine schedule.

Checklist for Managing Chronic HBV Infection

7 Steps to Care for Your Chronic HBV Patients

1. Help your patients understand their hepatitis B status

Make sure test results and letters are clear, and give your patient HBV informational brochures that are culturally and linguistically appropriate (p. 22).

2. Screen patients regularly for liver damage and cancer

See pages 15–16

People with chronic HBV infection can live completely normal lives as long as they are screened regularly for liver damage and cancer. Early detection and treatment will increase your patient's chance of long-term survival.

3. Give the hepatitis A vaccine

Hepatitis A is an infection of the liver caused by a different virus known as HAV (transmitted by contaminated food or water). Hepatitis A vaccination is therefore recommended for patients who already have chronic HBV infection to reduce the risk of further liver damage.

4. Tell your patients to avoid regular alcohol consumption

Alcohol is toxic to the liver and may accelerate the progression of liver damage to cirrhosis and liver failure. Drugs, herbal supplements and other substances with known liver toxicity should also be avoided.

5. Test and vaccinate your patients' close contacts

Your patient's family members and sexual partner(s) should be tested for HBsAg and anti-HBs (p. 7). This will help determine if they are 1) also chronically infected with HBV and need medical management, 2) vulnerable and need vaccination, or 3) already protected.

6. Educate your patients about how to minimize the risk of infecting others

Encourage the use of condoms, refraining from sharing toothbrushes or razors that could be contaminated with blood, and covering wounds. Advise your patients not to donate blood, organs, tissue or semen.

7. Give HBV treatment if indicated

See pages 17–18

Not everyone with HBV needs drug treatment, but medication may be appropriate for patients with high levels of both ALT and HBV DNA, patients with cirrhosis, or for patients receiving cancer chemotherapy.

Monitoring for Liver Damage

Order the ALT and AFP tests twice a year, and a liver ultrasound once a year.

Performing all 3 tests gives your patient the best chance for early detection and long-term survival.

Monitor for liver damage regularly

Many chronically infected persons show no symptoms and feel perfectly healthy, even though they may already have cirrhosis or be in the early stages of liver cancer. Therefore, it is important for physicians who see patients with chronic HBV infection to remain vigilant about monitoring for flare-up of the hepatitis, liver damage or cirrhosis, and to schedule regular screenings for liver cancer (p. 16).

Elevated ALT indicates liver damage.

ALT blood test – every 6 months

The ALT (alanine transaminase) test is one of the most useful and low cost tests to assess whether treatment against HBV is needed. An elevated ALT level is indicative of active liver damage. If ALT is normal, there is no evidence to support HBV treatment (unless patient is undergoing cancer chemotherapy, see p. 17).

HBV DNA indicates if liver damage is due to HBV, and helps evaluate treatment response.

HBV DNA level by PCR

The HBV DNA test is a direct measure of HBV viral load. If your patient's ALT level is elevated, the HBV DNA test will help verify whether his/her liver damage is caused by HBV infection, and determine whether HBV treatment is appropriate. HBV DNA levels that become undetectable or decrease significantly is a good measure of treatment response.

HBeAg and anti-HBe help monitor treatment response.

HBeAg and anti-HBe tests

HBeAg seroconversion, which is the loss of HBeAg (hepatitis B e antigen) and development of anti-HBe (hepatitis B e antibodies) is a sign of favorable response to treatment. This seroconversion can take years. The development of anti-HBe does not mean that your patient is cured and does not mean that treatment is unnecessary. The HBeAg test was also used as an indicator of HBV viral load before the HBV DNA test became widely available. Since some individuals carry mutant HBV strains that do not secrete HBeAg, the HBV DNA test is preferred when measuring HBV viral load.

Platelet count and albumin monitor for cirrhosis.

Platelet Count and Albumin

A low platelet count (generally less than 150,000 platelets/mm^3) combined with a low albumin level (3.5 gm/dL or lower), with or without prolonged prothrombin time, are signs suggestive of cirrhosis with impaired liver function.

Liver biopsies are seldom necessary unless performed as part of a clinical trial.

Screening for Liver Cancer

Screen for liver cancer regularly

The World Health Organization estimates that 70% of deaths associated with chronic HBV infection are due to hepatocellular carcinoma (HCC). Regular liver cancer screening involving both AFP and ultrasound tests is essential because *liver cancer can occur even in patients without cirrhosis*, and in the presence of normal ALT levels. AFP is elevated in only 40–60% of liver cancers. Ultrasound tests miss about 20% of liver cancers, especially in patients who are obese or have heterogeneous livers due to fatty liver or cirrhosis. Therefore, it is important for both tests to be performed regularly.

HCC (liver cancer) is the primary cause of death for patients with chronic hepatitis B.

Both the AFP and ultrasound tests must be done regularly because either test alone can miss the cancer.

AFP blood test – every 6 months

The AFP (alpha-fetoprotein) test is the most widely used blood test for liver cancer. A rising AFP level on serial measurements or an AFP level >500 ng/ml is usually associated with liver cancer (normal range is <10 ng/ml). Since AFP levels may appear normal in 40% of liver cancers, an ultrasound is needed to help detect tumors.

Ultrasound – every 12 months

Ultrasound is used to screen for liver tumors. Since use of ultrasound can catch only 80% of liver cancers, it must be performed along with the AFP test. If the ultrasound result is inconclusive (common in patients with cirrhosis or fatty liver) and your patient shows rising AFP levels, you should evaluate using a triphasic spiral CT scan of the liver or refer him/her for further assessment. A patient with a new lesion detected on ultrasound or CT scan, and/or rising AFP levels, should be referred immediately for liver cancer evaluation and treatment.

Increasing the fequency of liver cancer screenings

If your patient develops cirrhosis or has a family history of liver cancer, you should increase the frequency of AFP tests to every 3–4 months, and perform an ultrasound or triphasic spiral CT scan of the liver every 6 months.

Early Detection is Key

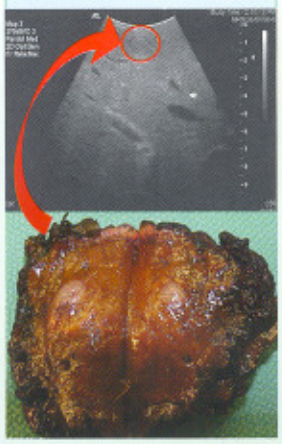
Liver cancer caused by chronic HBV infection often develops between 30 to 65 years of age, when people are maximally productive and have family responsibilities. It is reasonable to start regular screenings for chronic HBV patients at the age of 30 years or younger.

Late diagnosis of liver cancer is often the reason for the 6 to 12-month average survival time following diagnosis. It also explains the <10% 5-year survival rate of liver cancer patients. However, regular screening to detect the cancer while it is small can lead to successful treatment by surgical resection or liver transplantation, resulting in long-term survival.

Liver cancer screening is important because:

- Most patients have the appearance of perfect health, without showing any symptoms until it is already too late.
- Small tumor lumps are impossible to feel because of the shielded location of the liver underneath the ribs.
- Pain is uncommon until the tumor is very large. Even then, some tumors still do not cause pain.
- Liver cancers can grow rapidly.

1.2cm liver cancer detected by ultrasound screening and successfully removed. In this case AFP level was normal.



Drug Treatment for Chronic HBV Infection

Initiation of HBV treatment is appropriate if ALT and HBV DNA levels are elevated, your patient has cirrhosis, or he/she is undergoing cancer chemotherapy.

For a more detailed discussion of chronic HBV treatment, refer to the 2007 treatment guidelines developed by the American Association for the Study of Liver Diseases (Lok et al).

Rationale for treatment

Although **there is no cure for hepatitis B**, effective treatment can reduce liver damage and decrease the risk of cirrhosis and liver cancer.

Not every hepatitis B patient needs to be on treatment.
Regular screening for liver damage is necessary to determine if and when initiation of HBV treatment is appropriate (p. 15–16).

Patients should be informed about the treatment rationale, as well as options, side effects and risks associated with each treatment.

When is treatment for chronic HBV appropriate?

HBV treatment NOT indicated

Normal ALT (<30 U/L for men, <19 U/L for women)
There is no evidence to support treatment of these patients, regardless of their HBV DNA or HBeAg status. However, they are still at risk for liver cancer and flare up of hepatitis, and should be screened regularly (p. 15, 16).

Elevated ALT (>2x normal)
Low or undetectable HBV DNA
HBeAg (–)
Liver damage in these patients is not caused by HBV. You should investigate other possible causes for the elevated ALT, including hepatitis C virus infection, steatohepatitis (fatty liver), drug use or heavy alcohol consumption.

HBV treatment indicated

Elevated ALT (>2x normal)
Elevated HBV DNA (>20,000 IU/mL)
HBeAg (+)
These chronic HBV patients show signs of active liver damage associated with high viral activity, and it is reasonable to consider treatment by oral antivirals or injection immunostimulators (p. 18).

Elevated ALT (>2x normal)
Elevated HBV DNA (>20,000 IU/mL)
HBeAg (–)
These chronic HBVpatients show signs of active liver damage caused by a mutant strain of HBV that does not secrete HBeAg. It is reasonable to consider treatment by oral antivirals or injection immunostimulators (p. 18).

Cirrhosis
Detectable HBV DNA
For patients with compensated or decompensated cirrhosis consider HBV treatment by oral antivirals (p. 18), regardless of HBeAg status.

Cancer chemotherapy
When the immune system is suppressed during chemotherapy, flare-up of the HBV infection can lead to fulminant hepatitis and death. Therefore, HBsAg-positive patients undergoing chemotherapy should be placed on prophylactic oral antiviral treatment (p. 18), regardless of pre-treatment ALT, HBV DNA or HBeAg levels.

There are currently 6 FDA-approved drugs to treat chronic HBV infection

Oral Antivirals

Inhibit replication of HBV. Patient compliance in taking the medication daily is important to minimize the development of mutant or drug-resistant viruses.

- **Lamivudine** (Epivir-HBV, approved 1998)
  Pill or oral solution taken once a day.
- **Adefovir** (Hepsera, approved 2002)
  Pill taken once a day; need to monitor renal function (test for blood levels of blood urea nitrogen and creatinine).
- **Entecavir** (Baraclude, approved 2005)
  Pill or oral solution taken once a day.
- **Telbivudine** (Tyzeka, approved 2006)
  Pill taken once a day.

Injection Immunostimulators

Stimulate the immune system to kill liver cells infected with HBV. This class of drugs generally has a low response rate in patients with low pre-treatment ALT levels, high viral load and long duration of chronic infection (common in Asians). Not recommended for elderly patients and patients with decompensated cirrhosis.

- **Interferon alfa-2b** (Intron A, approved 1991)
  Administer by subcutaneous injection 3 times a week.
- **Peginterferon alfa-2a** (Pegasys, approved 2005)
  Administer by subcutaneous injection once a week.

Favorable responses to HBV treatment

- Sustained viral suppression: loss or marked reduction of HBV DNA levels (below detectable levels by PCR or <2000 IU/mL).
- Normalization of serum ALT levels.
- HBeAg seroconversion: loss of HBeAg, development of anti-HBe.
- Improvement in liver inflammation and fibrosis.
- Long-term reduction in the risk of liver cancer.

Note: There are no large-scale clinical studies that support combining the use of oral antivirals and injection immunostimulators in chronic HBV treatment.

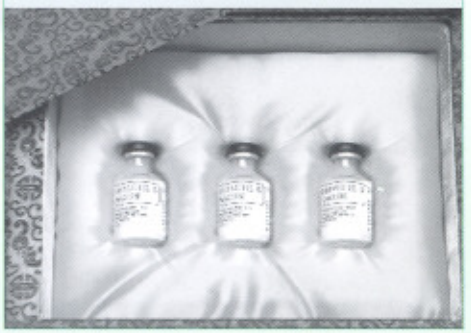
What are possible side effects?

For oral antivirals, the main adverse outcome is the development of drug-resistant mutant viruses. Side effects are uncommon and usually mild (e.g. weakness, headache, fatigue, diarrhea and stomach pain that may not be related to the medication). Adefovir has potential renal toxicity, though it is uncommon.

For injection immunostimulators, side effects may be severe and include flu-like symptoms (fevers, chills, headache, muscle pain), hair loss, leukopenia and psychiatric effects (mood swings, irritability, depression).

What about herbal treatments?

Herbal treatments have not been proven to prevent or treat HBV infection. The hepatitis B vaccine is the safest and most effective way to protect against HBV (p. 9–12).



Frequently Asked Questions

Q: My doctor told me that I have hepatitis B, but that I have normal liver function tests and am a "healthy carrier." What does this mean?

A: The term "healthy carrier" is misleading and should be discontinued. An HBV carrier is someone who has chronic HBV infection. Many chronically infected patients do not show symptoms and have normal liver function tests, but are still at increased risk for liver cancer and liver damage. Therefore, it is critical to remain vigilant about regular screening for liver damage (with ALT tests every 6 months) and liver cancer (with AFP tests every 6 months and an ultrasound every year).

Q: Isn't hepatitis B transmitted through contaminated food and water?

A: No. HBV is transmitted just like HIV: from an infected mother to her child at birth, through contaminated blood, or through unprotected sex. A different virus, the hepatitis A virus, is spread through food and water contaminated by human fecal waste.

Q: If I have hepatitis B, am I going to die from liver cancer or liver failure?

A: People with chronic hepatitis B can lead completely normal and active lives. With regular ALT and AFP tests every 6 months and an ultrasound every year, liver disease can be detected early and treated quickly to prevent further damage, which will increase the probability of long-term survival.

Q: If I am pregnant and have chronic hepatitis B, will my child be infected as well?

A: Hepatitis B is NOT a hereditary disease. Mothers who have chronic HBV infection can protect their newborns from becoming chronically infected with HBV if the newborn receives the first dose of the hepatitis B vaccine and the hepatitis B immune globulin (HBIG) shot at birth, and completes the hepatitis B vaccination series. This vaccination program will be more than 95% effective in preventing HBV transmission from the infected mother to her child.

Q: I have already received my 3-shot hepatitis B vaccination. Do I need a booster shot?

A: Currently, the CDC does not recommend a booster shot of the hepatitis B vaccine. Successful completion of the 3-shot vaccination series provides complete and lifelong protection against HBV in >95% of those vaccinated. For patients who do not have sufficient anti-HBs levels after vaccination, another 3-shot series should be administered with a different hepatitis B vaccine, and HBV status should be tested afterwards to confirm protection.

Q: Why is hepatitis B so common in Asians?

A: There is no clear explanation for the endemic persistence of HBV in Asia, though lack of symptoms, testing, vaccination, and awareness are all contributing factors. Because mother-to-child transmission is common in Asians, HBV infection is often passed silently from generation to generation. However, anyone (regardless of race or gender) without proper vaccination is susceptible to HBV infection.

Glossary of Key Terms

Abbreviations

AFP Alpha-fetoprotein. Elevated or rising AFP levels can indicate liver cancer.

ALT Alanine transaminase (or alanine aminotransferase). Elevated ALT levels can indicate active liver damage. Also referred to as SGPT (serum glutamate pyruvate transaminase).

Anti-HBc or HBcAb Hepatitis B core antibody. Its presence can indicate past or current infection with HBV. Not a protective antibody.

Anti-HBe or HBeAb Hepatitis B e antibody. Its presence can indicate a good response to the treatment of chronic hepatitis B. Not a protective antibody.

Anti-HBs or HBsAb Hepatitis B surface antibody. Levels ≥10 mIU/mL indicate protection against HBV.

HBeAg Hepatitis B e antigen. A marker of a high degree of HBV infectivity and indirect measure of viral load (though some mutant HBV strains have high viral load but negative HBeAg). Primarily used to monitor the response to HBV treatment.

HBIG Hepatitis B immune globulin. Provides short-term protection against HBV and is given in combination with the 3-dose hepatitis B vaccine, especially to unprotected individuals exposed to HBV or newborns born to chronically infected mothers.

HBsAg Hepatitis B surface antigen. Its presence for at least six months after initial infection indicates chronic HBV infection.

HBV DNA Hepatitis B virus deoxyribonucleic acid. The basis of the most direct blood test used to measure the hepatitis B viral load. It is used to assess and monitor the treatment of chronic HBV patients.

Terms

Acute HBV infection Initial infection with hepatitis B virus. May result in liver failure and sometimes death, but over 95% of adult cases will recover completely and develop immunity.

Chronic HBV infection Clinical term used to describe lifelong HBV infection, indicated by presence of hepatitis B surface antigen (HBsAg) in the blood for more than six months.

Cirrhosis Severe scarring of the liver that can lead to liver failure and death. Common causes include chronic hepatitis B, chronic hepatitis C and excessive alcohol consumption.

HBeAg seroconversion Loss of HBeAg and development of anti-HBe, a favorable response to HBV treatment.

Hepatitis General term meaning "inflammation of the liver," which can be caused by bacterial infections, trauma, adverse drug reactions, and a range of viruses including hepatitis A, B, C, D and E.

Hepatitis A Disease of the liver caused by infection with the hepatitis A virus (HAV). HAV is transmitted through food or water contaminated by fecal matter from humans infected with HAV. It is vaccine-preventable.

Hepatitis B Disease of the liver caused by infection with the hepatitis B virus (HBV). Chronic infection with HBV can lead to death caused by cirrhosis, liver failure or liver cancer. It is vaccine-preventable.

Hepatitis C Disease of the liver caused by infection with the hepatitis C virus (HCV). Largely a bloodborne infection that can also cause liver cancer and cirrhosis, but there is currently no vaccine.

Hepatocellular carcinoma (HCC) Most common type of malignant primary liver tumor, otherwise known as liver cancer. Worldwide, 60–80% of HCC is caused by HBV, and 15% by HCV. Cirrhosis due to long-term heavy alcohol consumption is also a common cause of HCC in the Western world.

Vaccination for HBV 3-shot vaccine series that provides >95% of individuals lifelong protection against HBV.

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